Elsevier Editorial System(tm) for European Neuropsychopharmacology
Manuscript Draft

Manuscript Number: ENP-16-121R1

Title: A systematic review and meta-analysis of randomised controlled trials of treatments for clozapine-induced obesity and metabolic syndrome

Article Type: Research article

Section/Category: CTHP - Clinical Trials and Human Pharmacology

Keywords: schizophrenia, clozapine, metabolic syndrome, treatment, meta-analysis

Corresponding Author: Dr. Jorge Zimbron, MBBS BSc(hons)

Corresponding Author's Institution: University of Cambridge

First Author: Jorge Zimbron, MBBS BSc(hons)

Order of Authors: Jorge Zimbron, MBBS BSc(hons); Golam M Khandaker, MBBS PhD; Chiara Toschi, BSc; Peter B Jones, MBBS, PhD; Emilio Fernandez-Egea, MD, PhD

Abstract: Metabolic complications are commonly found in people treated with clozapine. Reviews on the management of this problem have generally drawn conclusions by grouping different types of studies involving patients treated with various different antipsychotics. We carried out a systematic review and meta-analysis of pharmacological and non-pharmacological treatments for clozapine-induced obesity or metabolic syndrome. Two researchers independently searched PubMed and Embase for randomised controlled trials (RCTs) of treatments for clozapine-induced obesity or metabolic syndrome. All other types of studies were excluded. We only included RCTs where more than 50% of participants were taking clozapine.
We identified 15 RCTs. Effective pharmacological treatments for clozapine-induced obesity and metabolic syndrome include metformin, aripiprazole, and Orlistat (in men only). Meta-analysis of three studies showed a robust effect of metformin in reducing body mass index and waist circumference but no effects on blood glucose, triglyceride levels, or HDL levels. In addition, there is limited evidence for combined calorie restriction and exercise as a non-pharmacological alternative for the treatment of clozapine-induced obesity, but only in an in-patient setting. Rosiglitazone, topiramate, sibutramine, phenylpropanolamine, modafinil, and atomoxetine have not shown to be beneficial, despite reports of efficacy in other populations treated with different antipsychotics.
We conclude that randomised-controlled trial data support the use of metformin, aripiprazole, and Orlistat (in men only) for treating clozapine-induced obesity. Calorie restriction in combination with an exercise programme may be effective as a non-pharmacological alternative. Findings from trials in different populations should not be extrapolated to people being treated with clozapine.

*Revised Manuscript

A systematic review and meta-analysis of randomised controlled trials of treatments for clozapine-induced obesity and metabolic syndrome

Jorge Zimbron,[a,b*] Golam M Khandaker,[a,b*] Chiara Toschi,[c] Peter B Jones,[a] Emilio Fernandez-Egea [a,b,d]

[a] Department of Psychiatry, University of Cambridge, UK.

[b] Elizabeth House, Fulbourn Hospital, Fulbourn, Cambridge, CB21 5EF, UK.

[c] Department of Neuropsychiatry, University College London, Gower Street, London, WC1E 6BT, UK.

d Behavioural and Clinical Neuroscience Institute (BCNI), University of Cambridge.

* Joint first authors

Corresponding author: Dr. Jorge Zimbron

Elizabeth House, Fulbourn Hospital, Fulbourn, Cambridge, CB21 5EF

Tel: +44(0)1223 218832; E-mail: jz308@cam.ac.uk

Abstract:

Objective: To carry out a systematic review and meta-analysis of pharmacological and non-pharmacological treatments for clozapine-induced obesity or metabolic syndrome.

Methods: Two researchers independently searched PubMed and Embase for randomised controlled trials (RCTs) of treatments for clozapine-induced obesity or metabolic syndrome. All other types of studies were excluded. We only included RCTs where more than 50% of participants were taking clozapine.

Results: We identified 15 RCTs. Effective pharmacological treatments for clozapine-induced obesity and metabolic syndrome include metformin, aripiprazole, and Orlistat (in men only). Meta-analysis of three studies showed a robust effect of metformin in reducing body mass index and waist circumference but no effects on blood glucose, triglyceride levels, or HDL levels. In addition, there is limited evidence for combined calorie restriction and exercise as a non-pharmacological alternative for the treatment of clozapine-induced obesity, but only in an in-patient setting. Rosiglitazone, topiramate, sibutramine, phenylpropanolamine, modafinil, and atomoxetine have not shown to be beneficial, despite reports of efficacy in other populations.

Conclusion: Randomised-controlled trial data support the use of metformin, aripiprazole, and Orlistat (in men only) for treating clozapine-induced obesity. Calorie restriction in combination with an exercise programme may be effective as a non-pharmacological alternative. Findings from trials in different populations should not be extrapolated to people being treated with clozapine. Further trials focusing on clozapine-induced obesity and metabolic syndrome are needed.

Keywords: schizophrenia, clozapine, metabolic syndrome, treatment, meta-analysis

Abbreviations: BMI: Body mass index; CHAOS: Coronary artery disease, hypertension, atherosclerosis, obesity, and stroke; HbA1c: Glycosylated haemoglobin; HDL: High-density lipoprotein; Kg: kilogram; LDL: Low-density lipoprotein; RCT: Randomised controlled trial; VLDL: Very-low-density lipoprotein.

1 Introduction

Average life expectancy in people with schizophrenia is about 20 years shorter than the general population – this difference is largely attributed to increased mortality from chronic physical conditions such as heart disease and diabetes mellitus (Saha et al., 2007). Cardiometabolic complications such as weight gain, obesity, metabolic syndrome and diabetes mellitus are well recognized side effects of antipsychotics particularly the atypicals which are widely used today (De Hert et al., 2011).

Clozapine is generally regarded as the most efficacious antipsychotic drug (Leucht et al., 2013), but has been associated with the highest risk for developing obesity and metabolic complications compared with other atypical antipsychotics (Allison et al., 1999; Bodén et al., 2013; Gianfrancesco et al., 2002). It is estimated that the prevalence of metabolic syndrome in long-term clozapine users ranges from 28 to 45% (Bai et al., 2011; Bodén et al., 2013).

Clozapine has affinities for many receptors from multiple neurotransmitter systems. These include the dopamine (D1 – D5), serotonin (5-HT1A/1D, 5-HT2A/2C, 5-HT3, 5-HT6, and 5-HT7), histaminergic (H1 – H3), muscarinic (M1 – 5), adrenergic (α1-2 and β1-3), and GABAA receptors (Meltzer, 1994). The difference in the receptor binding profiles of different antipsychotics is thought to account for the different weight gain liabilities associated with them (Reynolds and Kirk, 2010). The weight gain induced by clozapine is highly variable and a twin study by Theisen and colleagues has shown that it is more highly correlated in monozygotic twins than in siblings, suggesting that genetic factors may play a major role (Theisen et al., 2005). More than 200 genes or markers have been linked to human obesity and many of them could be important in clozapine-induced obesity (Basile et al., 2001).

It has been hypothesised that clozapine causes obesity via its actions on the serotonergic and histaminergic systems. Rat studies have shown that 5-HT1A agonists and 5-HT2C/2A antagonists cause a marked increase in feeding (Yamada et al., 1996). Clozapine is a potent 5-HT2C/2A antagonist and a 5-HT1A partial agonist. H1 antagonism is known to be associated with increased feeding and weight gain, and antipsychotics with a high propensity for weight gain, like clozapine, have strong affinities for the H1 receptor (Wirshing et al., 1999). Two meta-analyses (De Luca et al., 2007; Sicard et al., 2010) have linked polymorphisms in the serotonergic system to clozapine-induced obesity, making it the most robust pharmacogenetic mechanism to date that could explain some of the variation in weight gain amongst these patients. Despite the evidence, it must be noted that some studies have not found such association(Basile et al., 2001; Rietschel et al., 1997; Yevtushenko et al., 2007). Results in studies looking at the histaminergic system have shown positive (Vehof et al., 2011) and negative (Hong et al., 2002) findings. Reviews of the literature (Basile et al., 2001; Lett et al., 2012; Müller et al., 2004; Reynolds, 2012) highlight many other targets that have been investigated in order to try to explain the variation in weight gain seen in people taking clozapine. The results of this research provide clues to the mechanisms behind clozapine-induced weight gain, but our understanding of this complex phenomenon is still limited and further research is warranted.

Clozapine is the gold standard for managing treatment-resistant schizophrenia, which comprises approximately 25% of all patients with this condition (Brenner et al., 1990). Clozapine is the only antipsychotic approved by the US Food and Drug Administration (FDA) for treatment-resistant schizophrenia (Novartis, 2002). Similarly, the UK national institute for health and care excellence (NICE) recommends clozapine as the treatment of choice for patients who do not respond to two antipsychotics (NICE, 2014). Clinicians, therefore, are faced with a difficult choice between efficacy and long-term cardiometabolic complications when choosing clozapine.

We present a systematic review and meta-analysis of pharmacological and non-pharmacological treatments for clozapine-induced obesity and metabolic syndrome. Previous reviews have considered the effect of weight loss treatments for patients who take antipsychotics (Faulkner et al., 2007, 2003; Maayan et al., 2010), but these have included studies of various different antipsychotics. Different antipsychotics have very different effects on weight gain and metabolic risk (Leucht et al., 2013), so there is a need to focus on particular antipsychotics in order to reduce heterogeneity. Given the different mechanisms of action of different antipsychotics, and their different metabolic effects, it is reasonable to suggest that treatments that may work with one antipsychotic, may not work with another. Whitney and colleagues have focused on clozapine (Whitney et al., 2015), but the review presented here is distinct in two ways. We report an up-to-date, systematic review and a meta-analysis (for metformin) of randomised controlled trials (RCTs) of pharmacological and other treatments for clozapine induced obesity and metabolic syndrome.

2 METHODS

2.1 Search Strategy

The PubMed and Embase electronic databases were searched from their inception until the 30th July, 2015 for all studies (without any filters) involving the management of obesity or metabolic syndrome in people taking clozapine using the following search terms: (clozapine OR norclozapine OR clozaril OR gen-clozapine OR analeptic OR leponex OR fazaclo OR froidir OR denzapine OR zaponex OR klozapol OR clopine) AND (obesity OR (weight AND gain) OR (high AND BMI) OR overweight OR obese OR (metabolic AND syndrome) OR (syndrome AND X) OR (cardiometabolic AND syndrome) OR (Reaven's AND syndrome)

OR CHAOS) AND (treatment OR programme OR management OR manage OR managing OR therapy OR diet OR regimen OR intervention OR trial OR (randomised AND controlled)). An automated search alerted the authors (JZ & CT) by email with any new articles published matching the search terms, which was in use up until December 2015. No further suitable articles were identified in this way. Reference lists of included studies and relevant review articles were hand searched. Two studies were added from this process (Fan et al., 2013; Henderson et al., 2011).

2.2 *Study selection*

Double-blind RCTs of interventions to address clozapine-induced obesity or metabolic syndrome were selected. Additionally, RCTs where blinding was not possible due to the nature of the treatment involved were also included. Studies where some participants were on other antipsychotics were included, provided that clozapine was prescribed to the majority (>50%) of the study participants and that separate analyses by antipsychotic type were conducted. Case reports, case series, and non-randomised trials were excluded.

2.3 *Data extraction*

Two researchers (JZ, CT) carried out the literature search, examined search results, applied selection criteria, and selected suitable articles independently by going through all titles and abstracts. A list was compiled after discussing potential articles for the review and the full text for each article was obtained. Any exclusion after this point was discussed on a case-by-case basis.

2.4 *Quality assessment of selected studies:*

All the studies included in this review were assessed for quality using the “Consolidated Standards of Reporting Trials (CONSORT) statement” checklist (Schulz et al., 2010). There are 25 items on the checklist, but some are subdivided into further items, giving a total maximum of 37 standards (not all of which are applicable to every study). We calculated a quality score for each study, which is the percentage of total applicable standards met by each study.

2.5 *Data Synthesis for Meta-Analysis*

Quantitative meta-analysis combined the outcomes of body mass index (BMI), waist circumference, serum glucose, high density lipoprotein (HDL) cholesterol, and triglycerides from three available trials of metformin as the active treatment (Carrizo et al., 2009; Chen et al., 2013; Hebrani et al., 2015). For each outcome, first we calculated mean change-from-baseline and its standard deviation (SD) for metformin and placebo groups at the end of follow-up. Then we calculated mean difference and 95% confidence intervals of mean change-from-baseline between groups, which were combined using fixed effect meta-analysis. Studies were weighted using inverse variance method. Heterogeneity between study samples was assessed using Chi-squared test. The I^2 statistic was calculated to express the fraction of variation between studies that was due to heterogeneity (Higgins et al., 2003). Because the length of follow-up varied between trials, we used measurements that were taken sufficiently close to each other between studies (Carrizo et al at 14 weeks; Chen et al and Hebrani et al at 16 weeks). When SD for mean change-from-baseline was not reported we used the values for the same outcome measure from other studies in the review. This approach is appropriate because the methods for measuring the main outcomes (BMI and waist circumference) were similar between studies, and so was the duration of follow-up. Meta-analysis was carried out using the software RevMan, version 5.3, freely available from the Cochrane collaboration database (Cochrane Informatics & Knowledge Management Department, 2015).

3 RESULTS

Figure 1 summarises the study selection process for this systematic review. The electronic database search yielded 2,370 articles. Twelve other articles were identified from a manual search. Screening of titles and abstracts identified 44 potentially suitable articles for the review, of which 29 were subsequently discarded after examination of full text versions (see online supplementary table for excluded studies).

[figure 1 here]

Fifteen studies met the selection criteria. These can be broadly divided into research looking at pharmacological, non-pharmacological, and combination of both pharmacological and non-pharmacological treatments. The key interventions and findings of these studies are summarised in Table 1.

3.1 Pharmacological Treatments

3.1.1 Meta-analysis of RCTs of Metformin

Three RCTs examined metformin as a sole treatment for clozapine-induced obesity and metabolic syndrome (Carrizo et al., 2009; Chen et al., 2013; Hebrani et al., 2015). These studies carried out a completer analysis of the data. Chen and colleagues did not report any participants failing to complete the study (Chen et al., 2013). Carrizo and colleagues reported that 7 participants (23%) in the treatment group did not complete the trial (Carrizo et al., 2009). Hebrani and colleagues had a large drop-out rate with 11 participants (37%) stopping the intervention, although 12 participants (40%) in the placebo group also failed to complete the study (Hebrani et al., 2015).

Metformin is an effective and widely used treatment for diabetes mellitus. It is a biguanide with antihyperglycaemic effects and is the most studied pharmacological agent for treating obesity and metabolic syndrome caused by antipsychotics in general (Fiedorowicz et al., 2012). It lowers both basal and postprandial plasma glucose, but it does not stimulate insulin secretion and, hence, does not produce hypoglycaemia.

3.1.1.1 Effect on BMI and Waist Circumference

Data on BMI and waist circumference were available from all three RCTs, totalling 71 participants in the metformin group and 75 participants in the placebo group. Metformin treatment was associated significant reductions in BMI and waist circumference (Figure 2, panels A & B). At the end of follow-up average BMI was about 1-point lower in the metformin group compared with the placebo group; mean difference -0.89 (95% CI, -1.20, -0.58); P<0.0001. There was no evidence for significant heterogeneity between studies (P=0.42; I^2=0%). Similarly, at the end of follow-up average waist circumference was about 2cms lower in the metformin group compared with the placebo group; mean difference -1.69 (95% CI, -2.84, -0.54); P=0.004. Again, no evidence for significant heterogeneity was found between studies (P=0.57; I^2=0%).

[Figure 2, Panels A-B]

3.1.1.2 Effect on Blood Glucose and Lipids

No significant difference between metformin and placebo groups was observed for blood glucose, HDL cholesterol and triglyceride levels (Figure 2, panels C-E).

[Figure 2, Panels C-E]

3.1.2 Rosiglitazone

Rosiglitazone is used in monotherapy or combination therapy in patients with diabetes mellitus. It works at the transcription factor level in cells that metabolise glucose and fat, with the net effect of lowering fasting and post-prandial blood glucose levels and HbA1c levels, without causing hypoglycaemia (Yki-Järvinen, 2004). Henderson and colleagues (Henderson et al., 2009) looked at the effect of rosiglitazone in a small group of participants (n=18) who were treated for 8 weeks. They found no difference in weight, BMI, waist circumference, waist-hip ratio, or body fat percentage between groups, but there was some evidence of a reduction in low-density lipoprotein (LDL) (effect size = 0.30; $p = 0.04$) in the treatment group.

3.1.3 Modafinil

Henderson and colleagues (Henderson et al., 2011) conducted a secondary analysis of a study (Freudenreich et al., 2009) looking at the effect of modafinil treatment for 8 weeks on weight gain, glucose, lipid metabolism, and diet. They found no significant differences between groups in terms of blood pressure, weight, BMI, glucose, insulin resistance, or lipid metabolism at the end of follow up.

3.1.4 Orlistat

Orlistat, a lipase inhibitor that reduces fat absorption from the intestines (Lucas and Kaplan-Machlis, 2001), is the only pharmacological treatment available that is not absorbed into the central nervous system.

Joffe and colleagues (Joffe et al., 2008) conducted a RCT looking at the effects of Orlistat on weight, fasting glucose, and blood lipids in a group of 63 patients being treated with clozapine (n = 50 [79%]) or olanzapine (n = 13 [11%]). The drop-out rates in this study were considerable with 7 patients in the treatment group (23%) and 7 in the placebo group (22%) failing to complete the study, but the researchers used intention-to-treat analyses to interpret the data. After 16 weeks, the only difference they found was a 2.3kg mean weight loss in men treated with Orlistat, but not in women. Five people (16.1%) were classified as ‘responders’ (>5% weight loss) in the treatment group vs. 2 (6.3%) in the placebo group, but the differences were not statistically significant (Fisher exact test, $p = 0.26$). The amount of weight loss seen is similar to that in trials of Orlistat in the non-psychiatric population (Padwal et al., 2004). Diarrhoea was the main reason for discontinuation of Orlistat (4 patients). In a subsequent publication of the same trial (Tchoukhine et al., 2011), they analysed the effects of administering Orlistat for a further 16 weeks to participants who completed the initial trial, but no additional benefit was found.

3.1.5 Topiramate

We found three trials looking at the effects on psychotic symptoms of adding the anticonvulsant topiramate to clozapine treatment (Afshar et al., 2009; Behdani et al., 2011; Muscatello et al., 2011). Weight loss was not the primary outcome and was simply highlighted as a side effect, hence only limited data is available and meta-analysis was not possible. Afshar and colleagues (Afshar et al., 2009) conducted an 8 week, double-blind, placebo controlled, randomised trial (n=32) where there was no effect of topiramate (300mg/day) on BMI observed. A significantly greater proportion of people in the topiramate group reported “weight loss” when compared with those given placebo (37.5% vs. 6.2% [$p \leq 0.05$]), although the amount of weight loss was not defined. No further information is available from the study.

The study of Muscatello and colleagues (Muscatello et al., 2011) mentions a 1kg difference in the topiramate group (200mg/day) after 24 weeks of treatment. The weight difference in the placebo group is not reported and the weight loss observed was not found to be statistically significant ($p = 0.236$).

Finally, Behdani and colleagues (Behdani et al., 2011) conducted a 17 week trial of augmenting clozapine with topiramate (200 - 300mg/day). They report that 15% (n= 6) of the topiramate group experienced 'weight loss' in comparison with 0% of the placebo group. Statistical analyses were not carried out and 'weight loss' is not defined.

3.1.6 *Sibutramine*

Sibutramine was introduced to the US in 1997 as a weight loss agent. It affects serotonin and noradrenaline re-uptake, and its hypophagic effect is thought to be mediated by activation of the 5-HT2C receptor. It has been withdrawn following evidence that it increases the risk of cardiovascular complications (European Medicines Agency, 2010). Following a trial showing sibutramine is effective for weight loss in olanzapine treated patients (Henderson et al., 2005), Henderson and colleagues carried out a 12 week, double-blind, placebo-controlled, randomised trial in 21 patients on clozapine (Henderson et al., 2007). They looked at changes from baseline in body weight, BMI, waist circumference, glucose, HbA1c, blood lipids, Positive and Negative Syndrome Scale (PANSS) scores, blood pressure, and heart rate, but found no significant difference on any these measures between groups.

3.1.7 *Phenylpropanolamine*

Phenylpropanolamine is an α1-agonist thought to act as an appetite suppressant by augmenting noradrenergic neurotransmission, which used to be sold over-the-counter as a treatment for obesity until it was discovered that it increases the risk of haemorrhagic stroke in women (Kernan et al., 2000). Borovicka and colleagues (Borovicka et al., 2002) carried out the only double-blind, RCT with this agent in 16 people taking clozapine. After 12 weeks, no difference was found between the treatment and the placebo group in terms of weight, glucose, HbA1c, or cholesterol levels.

3.1.8 *Aripiprazole*

We identified two studies of Aripiprazole, which were not meta-analysed due to differences in methods and duration of follow up. Fleischhacker and colleagues conducted a large, multi-centre study (n=207), to evaluate the effects of adding aripiprazole to clozapine (Fleischhacker et al., 2010). In a last observation carried forward analysis, they found that aripiprazole reduced weight (mean treatment difference of -2.15 kg), BMI (-0.8 kg/m^2), LDL cholesterol (-10.3 mg/dL), and waist circumference (-2.0 cm) after a treatment period of 16 weeks. There was no difference in PANSS scores between the treatment group and controls, but there were some improvements in the Clinical Global Impression (CGI) scale and in the Impressions and Investigator's Assessment questionnaire in the treatment group. In the placebo group 6 (6%) patients failed to complete the study and there were 11 (10%) drop-outs in those receiving aripiprazole, with 5 (5%) due to adverse events. Some of their results are supported by a more recent trial (n = 30) by Fan and colleagues (Fan et al., 2013). They looked at the effects of adding 15mg of aripiprazole to patients on clozapine for a period of 8 weeks. The treatment group showed significant reductions in plasma LDL levels, improved glucose effectiveness as measured by the frequently sampled intravenous glucose tolerance test, as well as a significant reduction in lean mass (-1.1 ± 1.6kg vs 0.6 ± 1.6kg in placebo) as measured by whole-body dual-energy X-ray absorptiometry. There were similar proportions of drop-outs in both arms of the study (4 in the placebo (22%) and 4 (20%) in the treatment group). It is not specified whether some of their data was used in the analysis or not.

3.2 *Non-Pharmacological treatments*

3.2.1 *Calorie restriction and exercise*

Wu and colleagues (Wu et al., 2007) carried out a 6 month RCT of exercise and calorie restriction versus treatment as usual in 53 inpatients with schizophrenia taking clozapine. The exercise component was designed to fit the hospital environment, and it consisted of three days per week of level walking (1.62km or ~40 minutes) together with walking up 231 stairs and down 330 stairs for 20 minutes under supervision (exercise energy expenditure per week = 600 – 750kcal). Dietary control consisted of 1300 – 1500kcal/day for women and 1600-1800kcal/day for men. The treatment group had reductions in BMI (- 1.59kg/m2), body weight (-4.2kg), hip (-3.3cm) and waist circumference (-3.3cm) after 6 months. They also had lower levels of triglycerides, insulin, and cortisol. No group differences were found in glucose and cholesterol levels. There were no drop-outs in the treatment group and only 3 (11%) in the control group.

3.3 <u>*Combination treatments*</u>

3.3.1 *Atomoxetine and Weight Watcher's Programme*

Atomoxetine is a selective norepinephrine reuptake inhibitor used in attention deficit hyperactivity disorder, which has been found to have appetite suppressant properties (Spencer et al., 1998). It has been postulated to improve cognitive impairments in schizophrenia, although scientific evidence for this idea is lacking (Friedman et al., 2008). In a 24 week double-blind randomised controlled trial (n=37), Ball and colleagues (Ball et al., 2011) tested whether atomoxetine could help achieve weight loss in clozapine (52% of sample) and olanzapine treated patients. All participants also undertook a 10 week 'Weight Watchers' programme (a weight loss programme mainly used in the US, UK, Ireland and Australia) which involved diet and exercise. No significant differences were found with regards to weight loss, LDL, HDL, triglycerides, very-low-density lipoprotein (VLDL), cognitive measures, or symptomatology between groups. Of interest, only 9 (24%) participants (6 on placebo and 3 on atomoxetine) who completed the study were adherent to the exercise programme, but the amount of weight loss they experienced ranged from <3% to 14% of their study baseline weight.

[Table 1 about here]

4 **Discussion**

Few RCTs looking at treatments for obesity and metabolic syndrome caused by clozapine are available. Our results suggest that adjuvant treatment with metformin, aripiprazole or Orlistat might be effective pharmacological strategies, albeit with limited clinical impact.

The evidence on metformin in clozapine-treated patients suggests that its use is likely to have a small beneficial effect with regards to body weight, blood lipids, and insulin levels. This is thought to be caused by its effects in enhancing the glycaemic control effects of insulin, antagonising glucagon, and suppressing gluconeogenesis and glycogenolysis (Wiernsperger and Bailey, 1999). Given the short duration of the follow-ups (6 months or less), it is not clear as to whether these changes eventually translate to clinically significant effects. One of the problems is that benefits seem to stop once metformin is withdrawn (Chen et al., 2013), therefore, treatment is likely to be required for life. Adverse effects can also occur and these resulted in 6 (20%) of the participants from one study discontinuing the drug (Hebrani et al., 2015). Metformin is also contraindicated in patients with ketosis-prone diabetes and underlying renal, hepatic, or cardiopulmonary disease (Wang et al., 2012).

Aripiprazole appears to be the only other agent with good evidence against obesity and metabolic syndrome induced by clozapine (Fan et al., 2013; Fleischhacker et al., 2010). Its effects on weight and cholesterol reduction are thought to be due to its partial agonist effects on 5-HT1A receptors and agonist effects on 5-HT2C receptors (Fan et al., 2013). Potential candidates need to be warned about the possibility of side effects, such as akathisia, which were observed in some study participants and accounted for nearly half of the drop-outs. It is still unclear whether any benefits continue after 7 months.

The results on rosiglitazone (Henderson et al., 2009), topiramate (Afshar et al., 2009), modafinil (Henderson et al., 2011), sibutramine (Henderson et al., 2007), phenylpropanolamine (Borovicka et al., 2002), and atomoxetine (Ball et al., 2011) are disappointing. The effects of Orlistat in body weight appear to be small, limited to men, with no further benefit after 16 weeks of use. Some participants also developed diarrhoea, which led to discontinuation of the treatment (Joffe et al., 2008). Some studies argue that the lack of effect in these agents may be due to a small sample size; however, even if larger samples managed to show statistical significance, the magnitude of the effects of these drugs in body weight and features of metabolic syndrome would still be small and unlikely to be of much clinical significance.

The effects of calorie restriction and exercise appear to be at least as good, if not better, than those of metformin and aripiprazole (Ball et al., 2011; Wu et al., 2007). The study by Wu and colleagues produced the best results, but the Chinese participants were all long-term inpatients under close scrutiny. They achieved a 90% completion rate in their six-month exercise programme without any significant incentives. In the UK, the median length of admission is 15 days and only 9.2% of patients are admitted for longer than 90 days (Thompson et al., 2004). Achieving that level of commitment in the community would be difficult, as can be seen in the US-based study by Ball and colleagues, where only 9 (24%) of participants completed the exercise programme, despite provision of free transport to the exercise sessions and incentives in the form of tokens that could be used to buy prizes at the end of the study. Nevertheless, every participant that finished the programme lost a substantial (~3 – 15.9kg) amount of weight (Ball et al., 2011).

This review shows that treatments that have been successful in 'atypical' antipsychotics can fail when tested in people taking clozapine. Positive weight loss trials with topiramate in people taking atypical antipsychotics (Ko et al., 2005) were not replicated in people treated with clozapine (Afshar et al., 2009). A positive trial of sibutramine in people taking olanzapine (Henderson et al., 2005) did not translate to clozapine (Henderson et al., 2007). A trial suggestive of modafinil having an impact in cholesterol levels of people treated with 'atypical antipsychotics' (Sudhakar et al., 2008) was not replicated in clozapine-treated patients (Henderson et al., 2011). The same applies for medication found to be helpful in the general population, as can be seen in the failure of phenylpropanolamine (Borovicka et al., 2002) and sibutramine (Henderson et al., 2007) in clozapine patients. The lack of an effect of these agents on clozapine-treated individuals may be due to different weight gain mechanisms given the different receptor affinities of clozapine.

Limiting the inclusion criteria of this review to randomised controlled trials favoured the inclusion of a small number of studies with a low risk of bias over a greater number of studies that would have been available, had other types of studies been considered. Given that clozapine has been continuously used for over 25 years, it was expected that a larger number of randomised controlled trials would have been carried out, but, unfortunately, this was not the case. The exclusion of all other types of evidence such as case reports and observational studies was done to try to eliminate bias. The limited information available on the topic, however, means that useful information may still be obtained from lower levels of evidence and the reader should consider looking at those studies that were excluded, as well as looking at more general reviews (Faulkner et al., 2007, 2003; Maayan et al., 2010; Whitney et al., 2015), in order to obtain a broader view of the evidence.

We conclude that there is evidence for pharmacological and non-pharmacological interventions that can help with the metabolic complications of clozapine treatment. The benefits of pharmacological interventions have to be weighed against potential side-effects and non-pharmacological alternatives can be effective but difficult to implement in community settings. The limited impact of all these interventions on clozapine-induced metabolic syndrome highlights the need for further research in this field.

5 Author Disclosure

5.1 Funding body agreements and policies

5.2 Contributors

JZ & EF designed the study and its protocol. JZ and CT carried out the literature search and data extraction. JZ, CT, and GK carried out the quality assessment of selected studies. GK carried out the meta-analysis. JZ wrote the first manuscript draft and all authors contributed to and have approved the final manuscript.

5.3 Conflict of interest

PBJ declares that, pro bono, he chaired an expert advisory group on early psychosis convened by the Otsuka-Lundbeck Alliance in December 2015. All other authors declare that they have no conflicts of interest.

5.4 Acknowledgements

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Figure legend

Figure 1. Study flow diagram for systematic review. PubMed and Embase were searched from their inception until 1st December, 2015. The key search terms used included 'randomised controlled trial', intervention, treatment, BMI, obesity, metabolic syndrome, and generic and proprietary terms for clozapine (see Methods).

Figure 2.

A: Meta-analysis of metformin on BMI.

B: Meta-analysis of metformin on waist circumference.

C: Meta-analysis of metformin on fasting blood glucose levels.

D: Meta-analysis of metformin on HDL cholesterol levels.

E Meta-analysis of metformin on triglyceride levels.

Study	Country	Treatment	n	% on clozapi ne	Population	Follow-up	Effects on weight (kg) and central obesity	Effects on Body Mass Index (kg/m2)	Effects on lipids	Effects on glucose	Effects on symptom s	CONSOR T Score*
Pharmacological Studies												
Carrizo (2009)	Venezue la	Metformin 500mg/day for 2 weeks, then 1000mg/day	61	100%	Out-patients	14 weeks	-1.87kg metformin vs. +0.16kg in placebo.	N/A	Increased HDL in treatment group.	Reduced insulin levels in treatment group.	No significan t changes in BPRS scores.	75%
Chen (2013)	China	Metformin 1500mg/day	55	100%	Out-patients. BMI >24 or metabolic abnormalitie s	24 weeks on treatme nt + 24 weeks without.	-3.2kg at 24 weeks (effect lost when metformin stopped).	-1.2 at 24 weeks (effect lost when metformin stopped)	Reduction in triglyceride s in metformin group.	Reduced fasting glucose in treatment group.	No significan t changes in PANSS scores.	80%
Hebrani (2015)	Iran	Metformin 500mg/day for 1 week, then 1000mg/day	37	100%	In-patients with a BMI >25	16 weeks on treatme nt + 4 weeks without.	- 1.7cm waist circumferenc e metformin vs. +1.0cm placebo.	-1.23 metformin vs. +0.01 placebo.	Reduced HDL	No difference s in fasting glucose levels.	No significan t changes in BPRS scores.	69%
Henderson (2009)	USA	Rosiglitazone 4mg/day	18	100%	Out-patients Insulin resistance or impaired glucose metabolism.	8 weeks	No significant difference in weight, weight circumferenc e or waist-hip ratio.	No significant difference s	Reduced small LDL particle in treatment group.	No significant changes.	No significan t changes in PANSS scores.	53%

Joffe (2008)	Finland	Orlistat 360mg/day	63	79%	90% inpatients, 10% outpatients receiving clozapine or olanzapine. BMI 28 - 43.	16 weeks	-2.36 kg Orlistat vs. +0.62kg placebo in men. Women did not benefit.	N/A	Reduced LDL in placebo.	No significant changes.	N/A	69%
Afshar (2009)	Iran	Topiramate 300mg/day with 25mg increments as required every 4 days	32	100%	Out-patients	8 weeks	Weight loss in 37.5% topiramate vs. 6.2% placebo. Exact figures N/A.	-0.91 topiramate +0.21 placebo	N/A	N/A	Reduction in all 3 categories of the PANSS in topiramate group.	64%
Behdani (2011)	Iran	Topiramate (200 – 300mg/day)	80	100%	In-patients	17 weeks	Weight loss in 15% topiramate vs. 0% placebo.	N/A	N/A	N/A	No significant changes in PANSS scores.	63%
Muscatello (2011)	Italy	Topiramate (200mg/day)	60	100%	Out-patients	24 weeks	-1.0 kg in topiramate group (placebo not reported)	N/A	N/A	N/A	No differences in BPRS. Bizarre behaviour reduction in topiramate group	63%

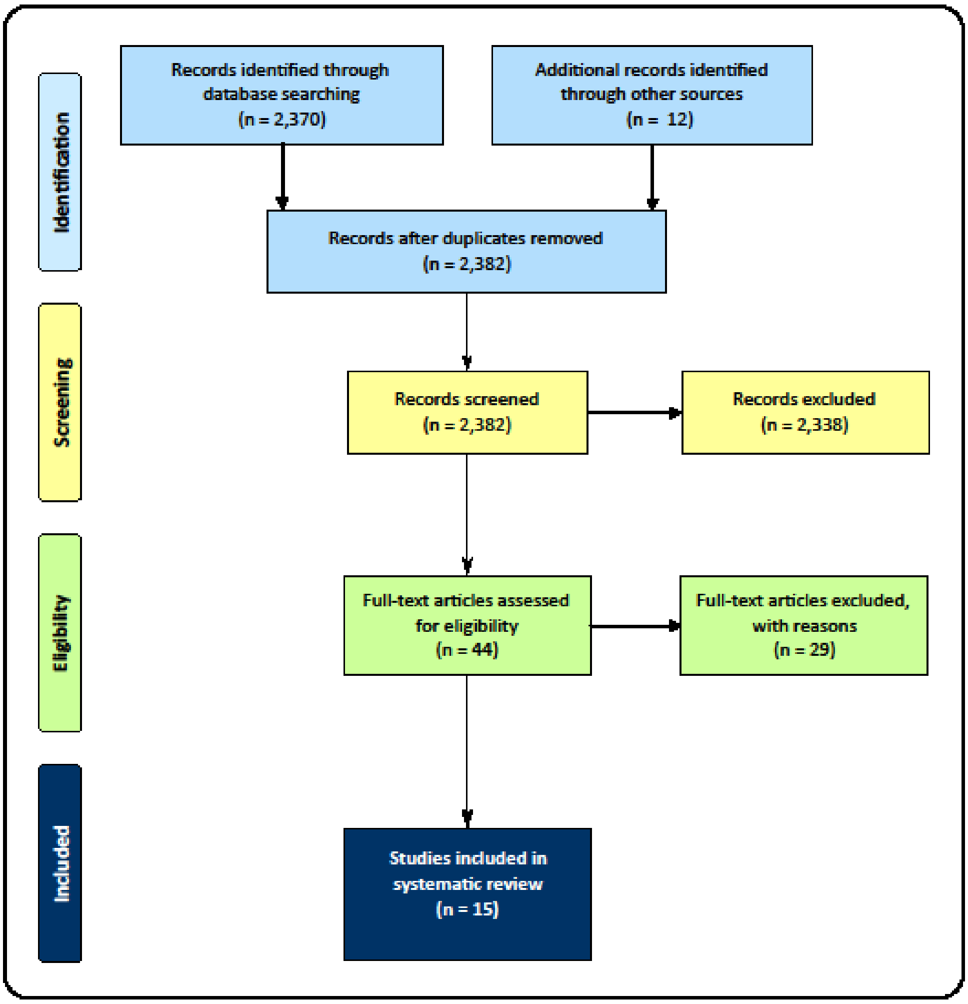
Henderson (2011)	USA	Modafinil 300mg/day	35	100%	Out-patients	8 weeks	No significant differences in weight	No significant differences	No significant differences	No significant differences in glucose levels or insulin resistance	No significant differences in negative symptoms or cognition	64%
Henderson (2007)	USA	Sibutramine 5-15mg/day	21	100%	Out-patients. BMI >30 or >27 with cardiovascular risk factors.	12 weeks	No significant differences in weight or waist circumference.	No significant differences	No significant changes.	No significant changes.	No significant changes in PANSS scores.	59%
Borovicka (2002)	USA	Phenylpropanolamine 75mg/day	16	100%	Out-patients. Gained >10% of baseline body weight	12 weeks	No significant differences in weight	N/A	No significant changes.	No significant changes.	No significant changes in PANSS scores.	55%
Fleischhacker (2010)	Multi-centre (10 European countries and South Africa)	Aripiprazole 5-15mg/day	207	100%	Out-patients. >2.5kg weight gain.	16 weeks + 12 weeks open-label extension	-2.53kg aripiprazole vs. -0.38kg placebo. -2cm waist circumference aripiprazole vs. 0cm placebo.	-0.8 aripiprazole vs. 0.0 placebo.	Reduced LDL and cholesterol in treatment group. No difference in triglycerides or HDL levels.	No significant changes.	No significant changes in PANSS scores.	81%

Fan (2013)	USA	Aripiprazole 15mg/day	30	100%	Out-patients	8 weeks	No difference in weight or waist circumference. Reduced lean mass in treatment group -1.1 ± 1.6kg aripiprazole vs 0.6 ± 1.6kg in placebo.	No significant differences	Reduced LDL plasma levels and LDL particle numbers in treatment group. No differences in cholesterol, HDL, or triglycerides.	Increased insulin-independent glucose clearance rate in treatment group.	No significant change in PANSS scores.	64%
	Non-Pharmacological Studies										
Wu (2007)	China	Calorie restriction (1300-1500kcal/day for women and 1600-1800 kcal/day for men) and exercise 3 times per week (600-750kcal of exercise per week)	53	100%	In-patients. BMI > 27.	6 months	-4.2kg treatment group vs. +1kg controls. -3.3cm hip and -3.3cm waist circumference treatment group vs. +0.3cm & +0.01cm controls.	-1.59 treatment group vs. +0.35 controls	Reduced triglycerides in treatment group.	Reduced insulin levels in treatment group.	N/A	58%
	Combination Studies										

Ball (2011)	USA	Atomoxetine 40-120mg/day + 10 week Weight Watchers Programme vs. Weight Watchers Programme alone.	37	52%	Gained 7% or more of baseline body weight.	24 weeks	No significant differences in weight.		No significant changes.	No significant changes.	No significant changes in BPRS scores.	62%

Table 1. Randomised controlled trials for obesity and metabolic syndrome in patients treated with clozapine. **The CONSORT score reflects the proportion of applicable standards according to the CONSORT checklist* (Schulz et al., 2010). *Higher scores reflect higher quality of trial reporting.*

Figure 1



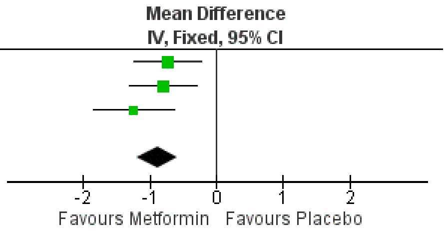
Identification
Screening
Eligibility
Included
Records identified through database searching (n = 2,370)
Additional records identified through other sources (n = 12)
Records after duplicates removed (n = 2,382)
Records screened (n = 2,382)
Records excluded (n = 2,338)
Full-text articles assessed for eligibility (n = 44)
Full-text articles excluded, with reasons (n = 29)
Studies included in systematic review (n = 15)

Figure 2

A

Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Carrizo 2009	-0.68	1	24	0.05	0.9	30	36.4%	-0.73 [-1.24, -0.22]
Chen 2013	-0.8	1	28	0	0.9	27	38.0%	-0.80 [-1.30, -0.30]
Hebrani 2015	-1.23	1	19	0.01	0.9	18	25.6%	-1.24 [-1.85, -0.63]
Total (95% CI)			**71**			**75**	**100.0%**	**-0.89 [-1.20, -0.58]**

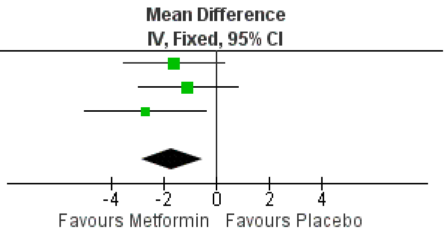
Heterogeneity: Chi² = 1.75, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 5.61 (P < 0.00001)



B

Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Carrizo 2009	-1.4	3.5	24	0.2	3.6	30	36.8%	-1.60 [-3.50, 0.30]
Chen 2013	-1.2	3.5	28	-0.1	3.6	27	37.8%	-1.10 [-2.98, 0.78]
Hebrani 2015	-1.7	3.5	19	1	3.6	18	25.4%	-2.70 [-4.99, -0.41]
Total (95% CI)			**71**			**75**	**100.0%**	**-1.69 [-2.84, -0.54]**

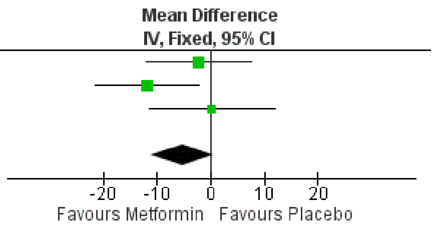
Heterogeneity: Chi² = 1.14, df = 2 (P = 0.57); I² = 0%
Test for overall effect: Z = 2.87 (P = 0.004)



C

Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Carrizo 2009	-0.1	18.4	24	2.2	18.3	30	36.7%	-2.30 [-12.15, 7.55]
Chen 2013	-13.1	18.4	28	-1.2	18.3	27	37.9%	-11.90 [-21.60, -2.20]
Hebrani 2015	-0.7	18.4	19	-0.9	18.3	18	25.5%	0.20 [-11.63, 12.03]
Total (95% CI)			**71**			**75**	**100.0%**	**-5.30 [-11.27, 0.67]**

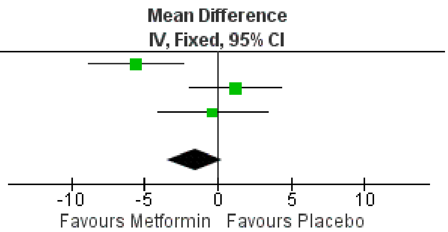
Heterogeneity: Chi² = 2.96, df = 2 (P = 0.23); I² = 33%
Test for overall effect: Z = 1.74 (P = 0.08)



D

Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Carrizo 2009	-3.8	7.5	24	1.8	3.7	30	34.9%	-5.60 [-8.88, -2.32]
Chen 2013	3.1	7.5	28	1.9	3.7	27	38.8%	1.20 [-1.91, 4.31]
Hebrani 2015	12.8	7.5	19	13.18	3.7	18	26.3%	-0.38 [-4.16, 3.40]
Total (95% CI)			**71**			**75**	**100.0%**	**-1.59 [-3.53, 0.35]**

Heterogeneity: Chi² = 9.23, df = 2 (P = 0.010); I² = 78%
Test for overall effect: Z = 1.61 (P = 0.11)



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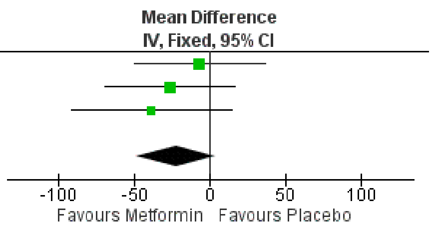
Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Carrizo 2009	-4.1	80	24	2.9	82.4	30	37.0%	-7.00 [-50.52, 36.52]
Chen 2013	-16.5	80	28	9.8	82.4	27	38.0%	-26.30 [-69.24, 16.64]
Hebrani 2015	-15.77	80	19	22.83	84.2	18	25.0%	-38.60 [-91.58, 14.38]
Total (95% CI)			**71**			**75**	**100.0%**	**-22.23 [-48.70, 4.25]**

Heterogeneity: Chi² = 0.87, df = 2 (P = 0.65); I² = 0%
Test for overall effect: Z = 1.65 (P = 0.10)



Supplementary Table

Studies excluded from the systematic review	
Study reference	**Reason for exclusion**
Henderson et al., 2005b; Kaye, 2003; Lin et al., 2005; Masopust et al., 2008; Ozenoglu et al., 2007; Pavlovic, 2005; Pigato et al., 2009; Schaefer et al., 2007; Weaver et al., 2010	Only provided data from case reports
Aquila and Emanuel, 2000; Cole et al., 2010; Hinze-Selch et al., 2000; Kalarchian et al., 2005; Kelly et al., 2006; Li et al., 2013; Reinstein et al., 1999; Schorr et al., 2008	Not randomised controlled trials
Daumit et al., 2013; Ghanizadeh et al., 2013; Khazaal et al., 2007; Ko et al., 2005; Wang et al., 2012; Wu et al., 2008	Patient populations taking multiple antipsychotics and the proportion of those taking clozapine was less than 50%
Fernández et al., 2012; Tchoukhine et al., 2011	Data was obtained from studies already included in this review
Chukhin et al., 2013; Fernández et al., 2010	Did not provide useful data on weight or metabolic abnormalities
Lu et al., 2004	Not blinded
Englisch and Zink, 2008	Review article

*Annotated Revised Manuscript

A systematic review and meta-analysis of randomised controlled trials of treatments for clozapine-induced obesity and metabolic syndrome

Jorge Zimbron,[a,b*] Golam M Khandaker,[a,b*] Chiara Toschi,[c] Peter B Jones,[a] Emilio Fernandez-Egea [a,b,d]

[a] Department of Psychiatry, University of Cambridge, UK.

[b] Elizabeth House, Fulbourn Hospital, Fulbourn, Cambridge, CB21 5EF, UK.

[c] Department of Neuropsychiatry, University College London, Gower Street, London, WC1E 6BT, UK.

d Behavioural and Clinical Neuroscience Institute (BCNI), University of Cambridge.

* Joint first authors

Corresponding author: Dr. Jorge Zimbron

Elizabeth House, Fulbourn Hospital, Fulbourn, Cambridge, CB21 5EF

Tel: +44(0)1223 218832; E-mail: jz308@cam.ac.uk

Abstract:

Objective: To carry out a systematic review and meta-analysis of pharmacological and non-pharmacological treatments for clozapine-induced obesity or metabolic syndrome.

Methods: Two researchers independently searched PubMed and Embase for randomised controlled trials (RCTs) of treatments for clozapine-induced obesity or metabolic syndrome. All other types of studies were excluded. We only included RCTs where more than 50% of participants were taking clozapine.

Results: We identified 15~~3~~ RCTs. Effective pharmacological treatments for clozapine-induced obesity and metabolic syndrome include metformin, aripiprazole, and Orlistat (in men only). Meta-analysis of three studies showed a robust effect of metformin in reducing body mass index and waist circumference but no effects on blood glucose, triglyceride levels, or HDL levels. In addition, there is limited evidence for combined calorie restriction and exercise as a non-pharmacological alternative for the treatment of clozapine-induced obesity, but only in an in-patient setting. Rosiglitazone, topiramate, sibutramine, phenylpropanolamine, modafinil, and atomoxetine have not shown to be beneficial, despite reports of efficacy in other populations.

Conclusion: Randomised-controlled trial data support the use of metformin, aripiprazole, and Orlistat (in men only) for treating clozapine-induced obesity. Calorie restriction in combination with an exercise programme may be effective as a non-pharmacological alternative. Findings from trials in different populations should not be extrapolated to people being treated with clozapine. Further trials focusing on clozapine-induced obesity and metabolic syndrome are needed.

Keywords: schizophrenia, clozapine, metabolic syndrome, treatment, meta-analysis

Abbreviations: BMI: Body mass index; CHAOS: Coronary artery disease, hypertension, atherosclerosis, obesity, and stroke; HbA1c: Glycosylated haemoglobin; HDL: High-density lipoprotein; Kg: kilogram; LDL: Low-density lipoprotein; RCT: Randomised controlled trial; VLDL: Very-low-density lipoprotein.

1 Introduction

Average life expectancy in people with schizophrenia is about 20 years shorter than the general population – this difference is largely attributed to increased mortality from chronic physical conditions such as heart disease and diabetes mellitus (Saha et al., 2007). Cardiometabolic complications such as weight gain, obesity, metabolic syndrome and diabetes mellitus are well recognized side effects of antipsychotics particularly the atypicals which are widely used today (De Hert et al., 2011).

Clozapine is generally regarded as the most efficacious antipsychotic drug (Leucht et al., 2013), but has been associated with the highest risk for developing obesity and metabolic complications compared with other atypical antipsychotics (Allison et al., 1999; Bodén et al., 2013; Gianfrancesco et al., 2002). It is estimated that the prevalence of metabolic syndrome in long-term clozapine users ranges from 28 to 45% (Bai et al., 2011; Bodén et al., 2013).

Clozapine has affinities for many receptors from multiple neurotransmitter systems. These include the dopamine (D1 – D5), serotonin (5-HT1A/1D, 5-HT2A/2C, 5-HT3, 5-HT6, and 5-HT7), histaminergic (H1 – H3), muscarinic (M1 – 5), adrenergic (α1-2 and β1-3), and GABAA receptors (Meltzer, 1994). The difference in the receptor binding profiles of different antipsychotics is thought to account for the different weight gain liabilities associated with them (Reynolds and Kirk, 2010). The weight gain induced by clozapine is highly variable and a twin study by Theisen and colleagues has shown that it is more highly correlated in monozygotic twins than in siblings, suggesting that genetic factors may play a major role (Theisen et al., 2005). More than 200 genes or markers have been linked to human obesity and many of them could be important in clozapine-induced obesity (Basile et al., 2001).

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It has been hypothesised that clozapine causes obesity via its actions on the serotonergic and histaminergic systems. Rat studies have shown that 5-HT1A agonists and 5-HT2C/2A antagonists cause a marked increase in feeding (Yamada et al., 1996). Clozapine is a potent 5-HT2C/2A antagonist and a 5-HT1A partial agonist. H1 antagonism is known to be associated with increased feeding and weight gain, and antipsychotics with a high propensity for weight gain, like clozapine, have strong affinities for the H1 receptor (Wirshing et al., 1999). Two meta-analyses (De Luca et al., 2007; Sicard et al., 2010) have linked polymorphisms in the serotonergic system to clozapine-induced obesity, making it the most robust pharmacogenetic mechanism to date that could explain some of the variation in weight gain amongst these patients. Despite the evidence, it must be noted that some studies have not found such association(Basile et al., 2001; Rietschel et al., 1997; Yevtushenko et al., 2007). Results in studies looking at the histaminergic system have shown positive (Vehof et al., 2011) and negative (Hong et al., 2002) findings. Reviews of the literature (Basile et al., 2001; Lett et al., 2012; Müller et al., 2004; Reynolds, 2012) highlight many other targets that have been investigated in order to try to explain the variation in weight gain seen in people taking clozapine. The results of this research provide clues to the mechanisms behind clozapine-induced weight gain, but our understanding of this complex phenomenon is still limited and further research is warranted.

Clozapine is the gold standard for managing treatment-resistant schizophrenia, which comprises approximately 25% of all patients with this condition (Brenner et al., 1990). Clozapine is the only antipsychotic approved by the US Food and Drug Administration (FDA) for treatment-resistant schizophrenia (Novartis, 2002). Similarly, the UK national institute for health and care excellence (NICE) recommends clozapine as the treatment of

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choice for patients who do not respond to two antipsychotics (NICE, 2014). Clinicians, therefore, are faced with a difficult choice between efficacy and long-term cardiometabolic complications when choosing clozapine.

We present a systematic review and meta-analysis of pharmacological and non-pharmacological treatments for clozapine-induced obesity and metabolic syndrome. Previous reviews have considered the effect of weight loss treatments for patients who take antipsychotics (Faulkner et al., 2007, 2003; Maayan et al., 2010), but these have included studies of various different antipsychotics. Different antipsychotics have very different effects on weight gain and metabolic risk (Leucht et al., 2013), so there is a need to focus on particular antipsychotics in order to reduce heterogeneity. Given the different mechanisms of action of different antipsychotics, and their different metabolic effects, it is reasonable to suggest that treatments that may work with one antipsychotic, may not work with another. Whitney and colleagues have focused on clozapine (Whitney et al., 2015), but the review presented here is distinct in two ways. We report an up-to-date, systematic review and a meta-analysis (for metformin) of randomised controlled trials (RCTs) of pharmacological and other treatments for clozapine induced obesity and metabolic syndrome.

2 METHODS

2.1 Search Strategy

The PubMed and Embase electronic databases were searched from their inception until the 30th July, 2015 for all studies (without any filters) involving the management of obesity or metabolic syndrome in people taking clozapine using the following search terms: (clozapine OR norclozapine OR clozaril OR gen-clozapine OR analeptic OR leponex OR fazaclo OR froidir OR denzapine OR zaponex OR klozapol OR clopine) AND (obesity OR (weight AND gain) OR (high AND BMI) OR overweight OR obese OR (metabolic AND syndrome) OR (syndrome AND X) OR (cardiometabolic AND syndrome) OR (Reaven's AND syndrome) OR CHAOS) AND (treatment OR programme OR management OR manage OR managing OR therapy OR diet OR regimen OR intervention OR trial OR (randomised AND controlled)). An automated search alerted the authors (JZ & CT) by email with any new articles published matching the search terms, which was in use up until December 2015. No further suitable articles were identified in this way. Reference lists of included studies and relevant review articles were hand searched. Two studies were added from this process (Fan et al., 2013; Henderson et al., 2011).

2.2 *Study selection*

Double-blind RCTs of interventions to address clozapine-induced obesity or metabolic syndrome were selected. Additionally, RCTs where blinding was not possible due to the nature of the treatment involved were also included. Studies where some participants were on other antipsychotics were included, provided that clozapine was prescribed to the majority (>50%) of the study participants and that separate analyses by antipsychotic type were conducted. Case reports, case series, and non-randomised trials were excluded.

2.3 *Data extraction*

Two researchers (JZ, CT) carried out the literature search, examined search results, applied selection criteria, and selected suitable articles independently by going through all titles and abstracts. A list was compiled after discussing potential articles for the review and the full text for each article was obtained. Any exclusion after this point was discussed on a case-by-case basis.

2.4 *Quality assessment of selected studies:*

All the studies included in this review were assessed for quality using the “Consolidated Standards of Reporting Trials (CONSORT) statement” checklist (Schulz et al., 2010). There are 25 items on the checklist, but some are subdivided into further items, giving a total maximum of 37 standards (not all of which are applicable to every study). We calculated a quality score for each study, which is the percentage of total applicable standards met by each study.

2.5 Data Synthesis for Meta-Analysis

Quantitative meta-analysis combined the outcomes of body mass index (BMI), waist circumference, serum glucose, high density lipoprotein (HDL) cholesterol, and triglycerides from three available trials of metformin as the active treatment (Carrizo et al., 2009; Chen et al., 2013; Hebrani et al., 2015). For each outcome, first we calculated mean change-from-baseline and its standard deviation (SD) for metformin and placebo groups at the end of follow-up. Then we calculated mean difference and 95% confidence intervals of mean change-from-baseline between groups, which were combined using fixed effect meta-analysis. Studies were weighted using inverse variance method. Heterogeneity between study samples was assessed using Chi-squared test. The I^2 statistic was calculated to express the fraction of variation between studies that was due to heterogeneity (Higgins et al., 2003). Because the length of follow-up varied between trials, we used measurements that were taken sufficiently close to each other between studies (Carrizo et al at 14 weeks; Chen et al and Hebrani et al at 16 weeks). When SD for mean change-from-baseline was not reported we used the values for the same outcome measure from other studies in the review. This approach is appropriate because the methods for measuring the main outcomes (BMI and waist circumference) were similar between studies, and so was the duration of follow-up. Meta-analysis was carried out using the software RevMan, version 5.3, freely available from the Cochrane collaboration database (Cochrane Informatics & Knowledge Management Department, 2015).

3 RESULTS

Figure 1 summarises the study selection process for this systematic review. The electronic database search yielded 2,370 articles. Twelve other articles were identified from a manual search. Screening of titles and abstracts identified 44 potentially suitable articles for the review, of which 29 were subsequently discarded after examination of full text versions (see online supplementary table for excluded studies).

[figure 1 here]

Fifteen studies met the selection criteria. These can be broadly divided into research looking at pharmacological, non-pharmacological, and combination of both pharmacological and non-pharmacological treatments. The key interventions and findings of these studies are summarised in Table 1.

3.1 *Pharmacological Treatments*

3.1.1 *Meta-analysis of RCTs of Metformin*

Three RCTs examined metformin as a sole treatment for clozapine-induced obesity and metabolic syndrome (Carrizo et al., 2009; Chen et al., 2013; Hebrani et al., 2015). These studies carried out a completer analysis of the data. Chen and colleagues did not report any participants failing to complete the study (Chen et al., 2013). Carrizo and colleagues reported that 7 participants (23%) in the treatment group did not complete the trial (Carrizo et al., 2009). Hebrani and colleagues had a large drop-out rate with 11 participants (37%) stopping the intervention, although 12 participants (40%) in the placebo group also failed to complete the study (Hebrani et al., 2015).

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Metformin is an effective and widely used treatment for diabetes mellitus. It is a biguanide with antihyperglycaemic effects and is the most studied pharmacological agent for treating obesity and metabolic syndrome caused by antipsychotics in general (Fiedorowicz et al., 2012). It lowers both basal and postprandial plasma glucose, but it does not stimulate insulin secretion and, hence, does not produce hypoglycaemia.

3.1.1.1 Effect on BMI and Waist Circumference

Data on BMI and waist circumference were available from all three RCTs, totalling 71 participants in the metformin group and 75 participants in the placebo group. Metformin treatment was associated significant reductions in BMI and waist circumference (Figure 2, panels A & B). At the end of follow-up average BMI was about 1-point lower in the metformin group compared with the placebo group; mean difference -0.89 (95% CI, -1.20, -0.58); P<0.0001. There was no evidence for significant heterogeneity between studies (P=0.42; I^2=0%). Similarly, at the end of follow-up average waist circumference was about 2cms lower in the metformin group compared with the placebo group; mean difference -1.69 (95% CI, -2.84, -0.54); P=0.004. Again, no evidence for significant heterogeneity was found between studies (P=0.57; I^2=0%).

[Figure 2, Panels A-B]

3.1.1.2 Effect on Blood Glucose and Lipids

No significant difference between metformin and placebo groups was observed for blood glucose, HDL cholesterol and triglyceride levels (Figure 2, panels C-E).

[Figure 2, Panels C-E]

3.1.2 Rosiglitazone

Rosiglitazone is used in monotherapy or combination therapy in patients with diabetes mellitus. It works at the transcription factor level in cells that metabolise glucose and fat, with the net effect of lowering fasting and post-prandial blood glucose levels and HbA1c levels, without causing hypoglycaemia (Yki-Järvinen, 2004). Henderson and colleagues (Henderson et al., 2009) looked at the effect of rosiglitazone in a small group of participants (n=18) who were treated for 8 weeks. They found no difference in weight, BMI, waist circumference, waist-hip ratio, or body fat percentage between groups, but there was some evidence of a reduction in low-density lipoprotein (LDL) (effect size = 0.30; p = 0.04) in the treatment group.

3.1.3 *Modafinil*

Henderson and colleagues (Henderson et al., 2011) conducted a secondary analysis of a study (Freudenreich et al., 2009) looking at the effect of modafinil treatment for 8 weeks on weight gain, glucose, lipid metabolism, and diet. They found no significant differences between groups in terms of blood pressure, weight, BMI, glucose, insulin resistance, or lipid metabolism at the end of follow up.

3.1.4 *Orlistat*

Orlistat, a lipase inhibitor that reduces fat absorption from the intestines (Lucas and Kaplan-Machlis, 2001), is the only pharmacological treatment available that is not absorbed into the central nervous system.

Joffe and colleagues (Joffe et al., 2008) conducted a RCT looking at the effects of Orlistat on weight, fasting glucose, and blood lipids in a group of 63 patients being treated with clozapine (n = 50 [79%]) or olanzapine (n = 13 [11%]). The drop-out rates in this study were considerable with 7 patients in the treatment group (23%) and 7 in the placebo group (22%) failing to complete the study, but the researchers used intention-to-treat analyses to interpret the data. After 16 weeks, the only difference they found was a 2.3kg mean weight loss in men treated with Orlistat, but not in women. Five people (16.1%) were classified as 'responders' (>5% weight loss) in the treatment group vs. 2 (6.3%) in the placebo group, but the differences were not statistically significant (Fisher exact test, p = 0.26). The amount of weight loss seen is similar to that in trials of Orlistat in the non-psychiatric population (Padwal et al., 2004). Diarrhoea was the main reason for discontinuation of Orlistat (4 patients). In a subsequent publication of the same trial (Tchoukhine et al., 2011), they analysed the effects of administering Orlistat for a further 16 weeks to participants who completed the initial trial, but no additional benefit was found.

3.1.5 Topiramate

~~There is one trial looking at the effects on psychotic symptoms of adding the anticonvulsant topiramate to clozapine treatment, where weight loss is mentioned (Afshar et al., 2009). In this 8 week, double-blind, placebo controlled, randomised trial (n=32) there was no effect of topiramate on BMI. A significantly greater proportion of people in the topiramate group reported "weight loss" when compared with those given placebo (37.5% vs. 6.2% [$p \leq 0.05$]), although the amount of weight loss was not defined. No further information is available from the study.~~We found three trials looking at the effects on psychotic symptoms of adding the anticonvulsant topiramate to clozapine treatment (Afshar et al., 2009; Behdani et al., 2011; Muscatello et al., 2011). Weight loss was not the primary outcome and was simply highlighted as a side effect, hence only limited data is available and meta-analysis was not possible. Afshar and colleagues (Afshar et al., 2009) conducted an 8 week, double-blind, placebo controlled, randomised trial (n=32) where there was no effect of topiramate (300mg/day) on BMI observed. A significantly greater proportion of people in the topiramate group reported "weight loss" when compared with those given placebo (37.5% vs. 6.2% [$p \leq 0.05$]), although the amount of weight loss was not defined. No further information is available from the study.

The study of Muscatello and colleagues (Muscatello et al., 2011) mentions a 1kg difference in the topiramate group (200mg/day) after 24 weeks of treatment. The weight difference in

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the placebo group is not reported and the weight loss observed was not found to be statistically significant ($p = 0.236$).

Finally, Behdani and colleagues (Behdani et al., 2011) conducted a 17 week trial of augmenting clozapine with topiramate (200 - 300mg/day). They report that 15% (n= 6) of the topiramate group experienced 'weight loss' in comparison with 0% of the placebo group. Statistical analyses were not carried out and 'weight loss' is not defined.

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3.1.6 Sibutramine

Sibutramine was introduced to the US in 1997 as a weight loss agent. It affects serotonin and noradrenaline re-uptake, and its hypophagic effect is thought to be mediated by activation of the 5-HT2C receptor. It has been withdrawn following evidence that it increases the risk of cardiovascular complications (European Medicines Agency, 2010). Following a trial showing sibutramine is effective for weight loss in olanzapine treated patients (Henderson et al., 2005), Henderson and colleagues carried out a 12 week, double-blind, placebo-controlled, randomised trial in 21 patients on clozapine (Henderson et al., 2007). They looked at changes from baseline in body weight, BMI, waist circumference, glucose, HbA1c, blood lipids, Positive and Negative Syndrome Scale (PANSS) scores, blood pressure, and heart rate, but found no significant difference on any these measures between groups.

3.1.7 Phenylpropanolamine

Phenylpropanolamine is an α1-agonist thought to act as an appetite suppressant by augmenting noradrenergic neurotransmission, which used to be sold over-the-counter as a treatment for obesity until it was discovered that it increases the risk of haemorrhagic stroke in women (Kernan et al., 2000). Borovicka and colleagues (Borovicka et al., 2002) carried out the only double-blind, RCT with this agent in 16 people taking clozapine. After 12 weeks, no difference was found between the treatment and the placebo group in terms of weight, glucose, HbA1c, or cholesterol levels.

3.1.8 *Aripiprazole*

We identified two studies of Aripiprazole, which were not meta-analysed due to differences in methods and duration of follow up. Fleischhacker and colleagues conducted a large, multi-centre study (n=207), to evaluate the effects of adding aripiprazole to clozapine (Fleischhacker et al., 2010). In a last observation carried forward analysis, t~~T~~hey found that aripiprazole reduced weight (mean treatment difference of -2.15 kg), BMI (-0.8 kg/m^2), LDL cholesterol (-10.3 mg/dL), and waist circumference (-2.0 cm) after a treatment period of 16 weeks. There was no difference in PANSS scores between the treatment group and controls, but there were some improvements in the Clinical Global Impression (CGI) scale and in the Impressions and Investigator's Assessment questionnaire in the treatment group. In the placebo group 6 (6%) patients failed to complete the study and there were 11 (10%) drop-outs in those receiving aripiprazole, with 5 (5%) due to adverse events. Some of their results are supported by a more recent trial (n = 30) by Fan and colleagues (Fan et al., 2013). They looked at the effects of adding 15mg of aripiprazole to patients on clozapine for a period of 8 weeks. The treatment group showed significant reductions in plasma LDL levels, improved glucose effectiveness as measured by the frequently sampled intravenous glucose tolerance test, as well as a significant reduction in lean mass (-1.1 ± 1.6kg vs 0.6 ± 1.6kg in placebo) as measured by whole-body dual-energy X-ray absorptiometry. There were similar proportions of drop-outs in both arms of the study (4 in the placebo (22%) and 4 (20%) in the treatment group). It is not specified whether some of their data was used in the analysis or not.

3.2 *Non-Pharmacological treatments*

3.2.1 *Calorie restriction and exercise*

Wu and colleagues (Wu et al., 2007) carried out a 6 month RCT of exercise and calorie restriction versus treatment as usual in 53 inpatients with schizophrenia taking clozapine. The exercise component was designed to fit the hospital environment, and it consisted of three days per week of level walking (1.62km or ~40 minutes) together with walking up 231 stairs and down 330 stairs for 20 minutes under supervision (exercise energy expenditure per week = 600 – 750kcal). Dietary control consisted of 1300 – 1500kcal/day for women and 1600-1800kcal/day for men. The treatment group had reductions in BMI (- 1.59kg/m2), body weight (-4.2kg), hip (-3.3cm) and waist circumference (-3.3cm) after 6 months. They also had lower levels of triglycerides, insulin, and cortisol. No group differences were found in glucose and cholesterol levels. There were no drop-outs in the treatment group and only 3 (11%) in the control group.

3.3 Combination treatments

3.3.1 *Atomoxetine and Weight Watcher's Programme*

Atomoxetine is a selective norepinephrine reuptake inhibitor used in attention deficit hyperactivity disorder, which has been found to have appetite suppressant properties (Spencer et al., 1998). It has been postulated to improve cognitive impairments in schizophrenia, although scientific evidence for this idea is lacking (Friedman et al., 2008). In a 24 week double-blind randomised controlled trial (n=37), Ball and colleagues (Ball et al., 2011) tested whether atomoxetine could help achieve weight loss in clozapine (52% of sample) and olanzapine treated patients. All participants also undertook a 10 week 'Weight Watchers' programme (a weight loss programme mainly used in the US, UK, Ireland and Australia) which involved diet and exercise. No significant differences were found with regards to weight loss, LDL, HDL, triglycerides, very-low-density lipoprotein (VLDL), cognitive measures, or symptomatology between groups. Of interest, only 9 (24%) participants (6 on placebo and 3 on atomoxetine) who completed the study were adherent to the exercise programme, but the amount of weight loss they experienced ranged from <3% to 14% of their study baseline weight.

[Table 1 about here]

4 Discussion

Few RCTs looking at treatments for obesity and metabolic syndrome caused by clozapine are available. Our results suggest that adjuvant treatment with metformin, aripiprazole or Orlistat might be effective pharmacological strategies, albeit with limited clinical impact.

The evidence on metformin in clozapine-treated patients suggests that its use is likely to have a small beneficial effect with regards to body weight, blood lipids, and insulin levels. This is thought to be caused by its effects in enhancing the glycaemic control effects of insulin, antagonising glucagon, and suppressing gluconeogenesis and glycogenolysis (Wiernsperger and Bailey, 1999). Given the short duration of the follow-ups (6 months or less), it is not clear as to whether these changes eventually translate to clinically significant effects. One of the problems is that benefits seem to stop once metformin is withdrawn (Chen et al., 2013), therefore, treatment is likely to be required for life. Adverse effects can also occur and these resulted in 6 (20%) of the participants from one study discontinuing the drug (Hebrani et al., 2015). Metformin is also contraindicated in patients with ketosis-prone diabetes and underlying renal, hepatic, or cardiopulmonary disease (Wang et al., 2012).

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Aripiprazole appears to be the only other agent with good evidence against obesity and metabolic syndrome induced by clozapine (Fan et al., 2013; Fleischhacker et al., 2010). Its effects on weight and cholesterol reduction are thought to be due to its partial agonist effects on 5-HT1A receptors and agonist effects on 5-HT2C receptors (Fan et al., 2013). Potential candidates need to be warned about the possibility of side effects, such as akathisia, which

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were observed in some study participants and accounted for nearly half of the drop-outs. It is still unclear whether any~~the~~ benefits continue after 7 months.

The results on rosiglitazone (Henderson et al., 2009), topiramate (Afshar et al., 2009), modafinil (Henderson et al., 2011), sibutramine (Henderson et al., 2007), phenylpropanolamine (Borovicka et al., 2002), and atomoxetine (Ball et al., 2011) are disappointing. The effects of Orlistat in body weight appear to be small, limited to men, with no further benefit after 16 weeks of use. Some participants also developed diarrhoea, which led to discontinuation of the treatment (Joffe et al., 2008). Some studies argue that the lack of effect in these agents may be due to a small sample size; however, even if larger samples managed to show statistical significance, the magnitude of the effects of these drugs in body weight and features of metabolic syndrome would still be small and unlikely to be of much clinical significance.

The effects of calorie restriction and exercise appear to be at least as good, if not better, than those of metformin and aripiprazole (Ball et al., 2011; Wu et al., 2007). The study by Wu and colleagues produced the best results, but the Chinese participants were all long-term inpatients under close scrutiny. They achieved a 90% completion rate in their six-month exercise programme without any significant incentives. In the UK, the median length of admission is 15 days and only 9.2% of patients are admitted for longer than 90 days (Thompson et al., 2004). Achieving that level of commitment in the community would be difficult, as can be seen in the US-based study by Ball and colleagues, where only 9 (24%) of participants completed the exercise programme, despite provision of free transport to the exercise sessions and incentives in the form of tokens that could be used to buy prizes at the end of the study. Nevertheless, every participant that finished the programme lost a substantial (~3 – 15.9kg) amount of weight (Ball et al., 2011).

This review shows that treatments that have been successful in ‘atypical’ antipsychotics can fail when tested in people taking clozapine. Positive weight loss trials with topiramate in people taking atypical antipsychotics (Ko et al., 2005) were not replicated in people treated with clozapine (Afshar et al., 2009). A positive trial of sibutramine in people taking olanzapine (Henderson et al., 2005) did not translate to clozapine (Henderson et al., 2007). A trial suggestive of modafinil having an impact in cholesterol levels of people treated with ‘atypical antipsychotics’ (Sudhakar et al., 2008) was not replicated in clozapine-treated patients (Henderson et al., 2011). The same applies for medication found to be helpful in the general population, as can be seen in the failure of phenylpropanolamine (Borovicka et al., 2002) and sibutramine (Henderson et al., 2007) in clozapine patients. The lack of an effect of these agents on clozapine-treated individuals may be due to different weight gain mechanisms given the different receptor affinities of clozapine.

Limiting the inclusion criteria of this review to randomised controlled trials favoured the inclusion of a small number of studies with a low risk of bias over a greater number of studies that would have been available, had other types of studies been considered. Given that clozapine has been continuously used for over 25 years, it was expected that a larger number of randomised controlled trials would have been carried out, but, unfortunately, this was not the case. The exclusion of all other types of evidence such as case reports and observational studies was done to try to eliminate bias. The limited information available on the topic, however, means that useful information may still be obtained from lower levels of evidence and the reader should consider looking at those studies that were excluded, as well as looking at more general reviews (Faulkner et al., 2007, 2003; Maayan et al., 2010; Whitney et al., 2015), in order to obtain a broader view of the evidence.

We conclude that there is evidence for pharmacological and non-pharmacological interventions that can help with the metabolic complications of clozapine treatment. The benefits of pharmacological interventions have to be weighed against potential side-effects and non-pharmacological alternatives can be effective but difficult to implement in community settings. The limited impact of all these interventions on clozapine-induced metabolic syndrome highlights the need for further research in this field.

5 Author Disclosure

5.1 Funding body agreements and policies

5.2 Contributors

JZ & EF designed the study and its protocol. JZ and CT carried out the literature search and data extraction. JZ, CT, and GK carried out the quality assessment of selected studies. GK carried out the meta-analysis. JZ wrote the first manuscript draft and all authors contributed to and have approved the final manuscript.

5.3 Conflict of interest

PBJ declares that, pro bono, he chaired an expert advisory group on early psychosis convened by the Otsuka-Lundbeck Alliance in December 2015. All other authors declare that they have no conflicts of interest.

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5.4 Acknowledgements

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Figure legend

Figure 1. Study flow diagram for systematic review. PubMed and Embase were searched from their inception until 1st December, 2015. The key search terms used included 'randomised controlled trial', intervention, treatment, BMI, obesity, metabolic syndrome, and generic and proprietary terms for clozapine (see Methods). ~~Figure 1. Study flow diagram for systematic review.~~

Figure 2.

A: Meta-analysis of metformin on BMI.

B: Meta-analysis of metformin on waist circumference.

C: Meta-analysis of metformin on fasting blood glucose levels.

D: Meta-analysis of metformin on HDL cholesterol levels.

E Meta-analysis of metformin on triglyceride levels.

Study	Country	Treatment	n	% on clozapine	Population	Follow-up	Effects on weight (kg) and central obesity	Effects on Body Mass Index (kg/m2)	Effects on lipids	Effects on glucose	Effects on symptoms	CONSORT Score*
Pharmacological Studies												
Carrizo (2009)	Venezuela	Metformin 500mg/day for 2 weeks, then 1000mg/day	61	100%	Out-patients	14 weeks	-1.87kg metformin vs. +0.16kg in placebo.	N/A	Increased HDL in treatment group.	Reduced insulin levels in treatment group.	No significant changes in BPRS scores.	75%
Chen (2013)	China	Metformin 1500mg/day	55	100%	Out-patients. BMI >24 or metabolic abnormalities	24 weeks on treatment + 24 weeks without.	-3.2kg at 24 weeks (effect lost when metformin stopped).	-1.2 at 24 weeks (effect lost when metformin stopped)	Reduction in triglycerides in metformin group.	Reduced fasting glucose in treatment group.	No significant changes in PANSS scores.	80%
Hebrani (2015)	Iran	Metformin 500mg/day for 1 week, then 1000mg/day	37	100%	In-patients with a BMI >25	16 weeks on treatment + 4 weeks without.	- 1.7cm waist circumference metformin vs. +1.0cm placebo.	-1.23 metformin vs. +0.01 placebo.	Reduced HDL	No differences in fasting glucose levels.	No significant changes in BPRS scores.	69%
Henderson (2009)	USA	Rosiglitazone 4mg/day	18	100%	Out-patients Insulin resistance or impaired glucose metabolism.	8 weeks	No significant difference in weight, weight circumference or waist-hip ratio.	No significant differences	Reduced small LDL particle in treatment group.	No significant changes.	No significant changes in PANSS scores.	53%

Joffe (2008)	Finland	Orlistat 360mg/day	63	79%	90% inpatients, 10% outpatients receiving clozapine or olanzapine. BMI 28 - 43.	16 weeks	-2.36 kg Orlistat vs. +0.62kg placebo in men. Women did not benefit.	N/A	Reduced LDL in placebo.	No significant changes.	N/A	69%
Afshar (2009)	Iran	Topiramate 300mg/day with 25mg increments as required every 4 days	32	100%	Out-patients	8 weeks	Weight loss in 37.5% topiramate vs. 6.2% placebo. Exact figures N/A.	-0.91 topiramate +0.21 placebo	N/A	N/A	Reduction in all 3 categories of the PANSS in topiramate group.	64%
Behdani (2011)	Iran	Topiramate (200 – 300mg/day)	80	100%	In-patients	17 weeks	Weight loss in 15% topiramate vs. 0% placebo.	N/A	N/A	N/A	No significant changes in PANSS scores.	63%
Muscatello (2011)	Italy	Topiramate (200mg/day)	60	100%	Out-patients	24 weeks	-1.0 kg in topiramate group (placebo not reported)	N/A	N/A	N/A	No differences in BPRS. Bizarre behaviour reduction in topiramate group	63%

Henderson (2011)	USA	Modafinil 300mg/day	35	100%	Out-patients	8 weeks	No significant differences in weight	No significant differences	No significant differences	No significant differences in glucose levels or insulin resistance	No significant differences in negative symptoms or cognition	64%
Henderson (2007)	USA	Sibutramine 5-15mg/day	21	100%	Out-patients. BMI >30 or >27 with cardiovascular risk factors.	12 weeks	No significant differences in weight or waist circumference.	No significant differences	No significant changes.	No significant changes.	No significant changes in PANSS scores.	59%
Borovicka (2002)	USA	Phenylpropanolamine 75mg/day	16	100%	Out-patients. Gained >10% of baseline body weight	12 weeks	No significant differences in weight	N/A	No significant changes.	No significant changes.	No significant changes in PANSS scores.	55%
Fleischhacker (2010)	Multi-centre (10 European countries and South Africa)	Aripiprazole 5-15mg/day	207	100%	Out-patients. >2.5kg weight gain.	16 weeks + 12 weeks open-label extension	-2.53kg aripiprazole vs. -0.38kg placebo. -2cm waist circumference aripiprazole vs. 0cm placebo.	-0.8 aripiprazole vs. 0.0 placebo.	Reduced LDL and cholesterol in treatment group. No difference in triglycerides or HDL levels.	No significant changes.	No significant changes in PANSS scores.	81%

Fan (2013)	USA	Aripiprazole 15mg/day	30	100%	Out-patients	8 weeks	No difference in weight or waist circumference. Reduced lean mass in treatment group -1.1 ± 1.6kg aripiprazole vs 0.6 ± 1.6kg in placebo.	No significant differences	Reduced LDL plasma levels and LDL particle numbers in treatment group. No differences in cholesterol, HDL, or triglycerides.	Increased insulin-independent glucose clearance rate in treatment group.	No significant change in PANSS scores.	64%
Non-Pharmacological Studies												
Wu (2007)	China	Calorie restriction (1300-1500kcal/day for women and 1600-1800 kcal/day for men) and exercise 3 times per week (600-750kcal of exercise per week)	53	100%	In-patients. BMI > 27.	6 months	-4.2kg treatment group vs. +1kg controls. -3.3cm hip and -3.3cm waist circumference treatment group vs. +0.3cm & +0.01cm controls.	-1.59 treatment group vs. +0.35 controls	Reduced triglycerides in treatment group.	Reduced insulin levels in treatment group.	N/A	58%
Combination Studies												

Ball (2011)	USA	Atomoxetine 40-120mg/day + 10 week Weight Watchers Programme vs. Weight Watchers Programme alone.	37	52%	Gained 7% or more of baseline body weight.	24 weeks	No significant differences in weight.		No significant changes.	No significant changes.	No significan t changes in BPRS scores.	62%

Table 1. Randomised controlled trials for obesity and metabolic syndrome in patients treated with clozapine. **The CONSORT score reflects the proportion of applicable standards according to the CONSORT checklist* (Schulz et al., 2010). *Higher scores reflect higher quality of trial reporting.*

Figure 1

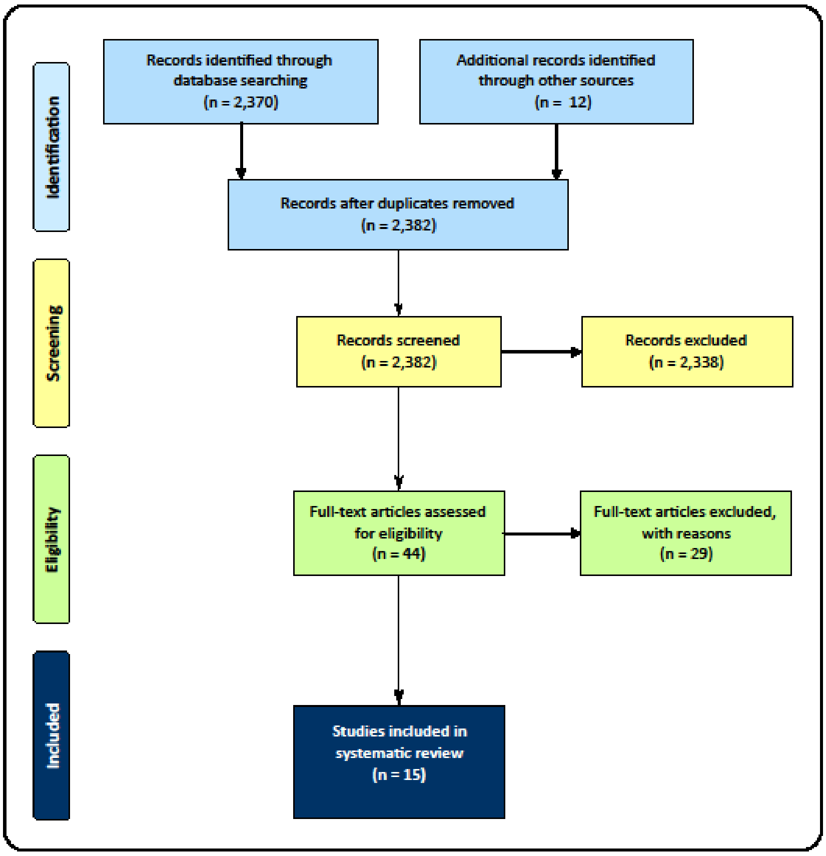

Identification
Screening
Eligibility
Included
Records identified through database searching (n = 2,370)
Additional records identified through other sources (n = 12)
Records after duplicates removed (n = 2,382)
Records screened (n = 2,382)
Records excluded (n = 2,338)
Full-text articles assessed for eligibility (n = 44)
Full-text articles excluded, with reasons (n = 29)
Studies included in systematic review (n = 15)

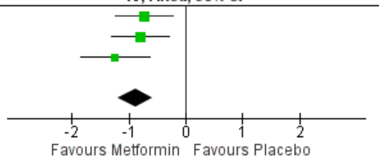
Figure 2

A

Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Carrizo 2009	-0.68	1	24	0.05	0.9	30	36.4%	-0.73 [-1.24, -0.22]
Chen 2013	-0.8	1	28	0	0.9	27	38.0%	-0.80 [-1.30, -0.30]
Hebrani 2015	-1.23	1	19	0.01	0.9	18	25.6%	-1.24 [-1.85, -0.63]
Total (95% CI)			**71**			**75**	**100.0%**	**-0.89 [-1.20, -0.58]**

Heterogeneity: Chi² = 1.75, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 5.61 (P < 0.00001)

Mean Difference IV, Fixed, 95% CI

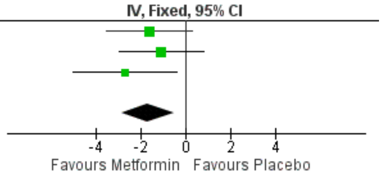


B

Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Carrizo 2009	-1.4	3.5	24	0.2	3.6	30	36.8%	-1.60 [-3.50, 0.30]
Chen 2013	-1.2	3.5	28	-0.1	3.6	27	37.8%	-1.10 [-2.98, 0.78]
Hebrani 2015	-1.7	3.5	19	1	3.6	18	25.4%	-2.70 [-4.99, -0.41]
Total (95% CI)			**71**			**75**	**100.0%**	**-1.69 [-2.84, -0.54]**

Heterogeneity: Chi² = 1.14, df = 2 (P = 0.57); I² = 0%
Test for overall effect: Z = 2.87 (P = 0.004)

Mean Difference IV, Fixed, 95% CI

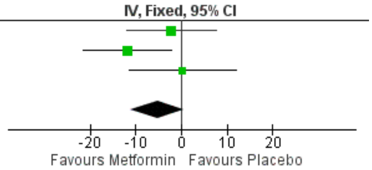


C

Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Carrizo 2009	-0.1	18.4	24	2.2	18.3	30	36.7%	-2.30 [-12.15, 7.55]
Chen 2013	-13.1	18.4	28	-1.2	18.3	27	37.9%	-11.90 [-21.60, -2.20]
Hebrani 2015	-0.7	18.4	19	-0.9	18.3	18	25.5%	0.20 [-11.63, 12.03]
Total (95% CI)			**71**			**75**	**100.0%**	**-5.30 [-11.27, 0.67]**

Heterogeneity: Chi² = 2.96, df = 2 (P = 0.23); I² = 33%
Test for overall effect: Z = 1.74 (P = 0.08)

Mean Difference IV, Fixed, 95% CI

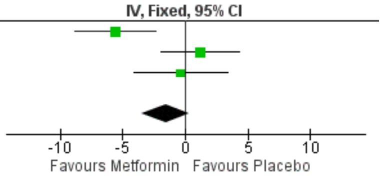


D

Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Carrizo 2009	-3.8	7.5	24	1.8	3.7	30	34.9%	-5.60 [-8.88, -2.32]
Chen 2013	3.1	7.5	28	1.9	3.7	27	38.8%	1.20 [-1.91, 4.31]
Hebrani 2015	12.8	7.5	19	13.18	3.7	18	26.3%	-0.38 [-4.16, 3.40]
Total (95% CI)			**71**			**75**	**100.0%**	**-1.59 [-3.53, 0.35]**

Heterogeneity: Chi² = 9.23, df = 2 (P = 0.010); I² = 78%
Test for overall effect: Z = 1.61 (P = 0.11)

Mean Difference IV, Fixed, 95% CI

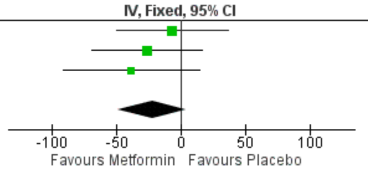


E

Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Carrizo 2009	-4.1	80	24	2.9	82.4	30	37.0%	-7.00 [-50.52, 36.52]
Chen 2013	-16.5	80	28	9.8	82.4	27	38.0%	-26.30 [-69.24, 16.64]
Hebrani 2015	-15.77	80	19	22.83	84.2	18	25.0%	-38.60 [-91.58, 14.38]
Total (95% CI)			**71**			**75**	**100.0%**	**-22.23 [-48.70, 4.25]**

Heterogeneity: Chi² = 0.87, df = 2 (P = 0.65); I² = 0%
Test for overall effect: Z = 1.65 (P = 0.10)

Mean Difference IV, Fixed, 95% CI



Supplementary Table

Studies excluded from the systematic review	
Study reference	**Reason for exclusion**
Henderson et al., 2005b; Kaye, 2003; Lin et al., 2005; Masopust et al., 2008; Ozenoglu et al., 2007; Pavlovic, 2005; Pigato et al., 2009; Schaefer et al., 2007; Weaver et al., 2010	Only provided data from case reports
Aquila and Emanuel, 2000; Cole et al., 2010; Hinze-Selch et al., 2000; Kalarchian et al., 2005; Kelly et al., 2006; Li et al., 2013; Reinstein et al., 1999; Schorr et al., 2008	Not randomised controlled trials
Daumit et al., 2013; Ghanizadeh et al., 2013; Khazaal et al., 2007; Ko et al., 2005; Wang et al., 2012; Wu et al., 2008	Patient populations taking multiple antipsychotics and the proportion of those taking clozapine was less than 50%
Fernández et al., 2012; Tchoukhine et al., 2011	Data was obtained from studies already included in this review
Chukhin et al., 2013; Fernández et al., 2010	Did not provide useful data on weight or metabolic abnormalities
Lu et al., 2004	Not blinded
Englisch and Zink, 2008	Review article

Role of the funding source

The authors did not receive funding from any research funding body for the preparation of this work.

Contributors

JZ & EF designed the study and its protocol. JZ and CT carried out the literature search and data extraction. JZ, CT, and GK carried out the quality assessment of selected studies. GK carried out the meta-analysis. JZ wrote the first manuscript draft and all authors contributed to and have approved the final manuscript.

Conflict of interest

PBJ declares that, pro bono, he chaired an expert advisory group on early psychosis convened by the Otsuka-Lundbeck Alliance in December 2015. All other authors declare that they have no conflicts of interest.

Acknowledgements

The authors would like to than Professor Thomas Barnes, for some helpful suggestions in the initial stages of the preparation of this work.